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Impact of meteorological factors on hemorrhagic fever with renal syndrome in 19 cities in China, 2005–2014

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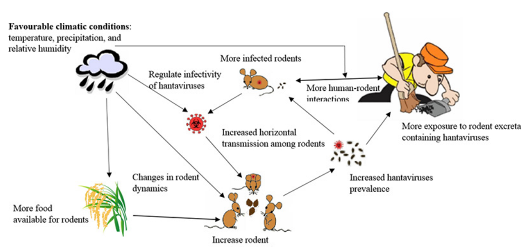
HIGHLIGHTS

- Weather variability plays a significant role in HFRS transmission in China.
- A 1 °C increase in maximum temperature resulted in 1.6% increase in HFRS.
- A 1 mm increase of weekly precipitation was associated with 0.2% increase in HFRS.
- HFRS-weather associations and lagged effects vary by region.
- Lagged effects did not end after an epidemic season but waned gradually.

GRAPHICAL ABSTRACT



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ABSTRACT

This study aims to investigate the associations between meteorological factors and hemorrhagic fever with renal syndrome (HFRS) in 19 cities selected from HFRS high risk areas across different climate zones in three Provinces of China. De-identified daily reports of HFRS in Anhui, Heilongjiang, and Liaoning Provinces for 2005–2014 were obtained from the Chinese Center for Disease Control and Prevention. Daily weather data from each study location were obtained from the China meteorological Data Sharing Service System. Generalised estimating equation models (GEE) were used to quantify the city-specific HFRS-weather associations. Multivariate random-effects meta-regression models were used to pool the city-specific HFRS-weather effect estimates. HFRS showed an overall downward trend during the study period with a slight rebound after 2010. Meteorological factors were significantly associated with HFRS incidence. HFRS was relatively more sensitive to weather variability in subtropical regions (Anhui Province) than in temperate regions (Heilongjiang and Liaoning Provinces). The size of effect estimates and the duration of lagged effects varied by locations. Pooled results of the 19 cities showed that a 1 °C increase in maximum temperature (T_{max}) resulted in a 1.6% (95% CI: 1.0%–2.2%) increase in HFRS; a 1 mm increase in weekly precipitation was associated with 0.2% (95%CI: 0.1%–0.3%) increase in HFRS; a 1% increase in average relative humidity was associated with a 0.9% (95%CI: 0.5%–1.2%) increase in HFRS. The lags with the largest effects for T_{max}, precipitation, and relative humidity occurred in weeks 29, 22, and 16, respectively. Lagged effects of meteorological factors did not end after an epidemic season but waned gradually in

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the following 3–4 epidemic seasons. Weather variability plays a significant role in HFRS transmission in China. The long duration of lagged effects indicates the necessity of continuous interventions following the epidemics.

1. Introduction

Hemorrhagic fever with renal syndrome (HFRS), a rodent-borne zoonotic disease caused by hantaviruses, is characterized by fever, headache, back and abdominal pain, hemorrhagic manifestations and renal dysfunction (Zhang et al., 2010). Transmission of the viruses to humans is mainly due to inhalation of, and/or contact with, virus-contaminated rodent excreta (e.g. urine, faeces, and saliva). China is one of the foremost countries seriously affected by HFRS, accounting for about 90% of global cases (Huang et al., 2012). The disease has been reported in almost all 31 provinces of mainland China, except Tibet, and it is endemic in 28 of these (Zhang et al., 2014). The morbidity and mortality of HFRS have declined significantly in the past decades mainly due to effective rodent surveillance and control, intensified vaccination programmes in high-endemic regions since 2008, and remarkably improved living and working conditions (Zhang et al., 2010; Zou et al., 2016; Li et al., 2014). However, HFRS still remains a serious public health problem in China, with 8853 new cases reported in 2016 leading to 48 deaths (National Health and Family Planning Commission of the People's Republic of China, 2016).

Hantaviruses are single-stranded, enveloped RNA viruses of the *Bunyaviridae* family. Of the seven sero/genotypes of hantaviruses identified in China (Zhang et al., 2010), Hantaan virus (HTNV) and Seoul virus (SEOV) are the two predominant agents, the former being responsible for up to 70% of cases. The main natural reservoir hosts of HTNV and SEOV are the striped field mouse (*Apodemus agrarius*) and the brown Norway rat (*Rattus norvegicus*), respectively (Hansen et al., 2015).

HFRS is a climate-sensitive infectious disease. Weather variability can influence HFRS directly and indirectly by affecting rodent population dynamics (e.g. reproductive rates and incubation periods), yields of crops which act as food sources for rodents, human-rodent interaction, and viral exposure opportunities in susceptible populations (Hansen et al., 2015; Sanfeliu, 2012) (see Fig. 1). Previous studies found that the effects of weather variability were usually delayed for 1 to 6 months (lagged effect) (Hansen et al., 2015). HFRS seasonality in China is generally characterized by a bimodal seasonal case distribution, with a rapid peak in winter and a longer lasting peak (about three months) in spring (Huang et al., 2012; Hansen et al., 2015). Moreover, interannual cycles of HFRS outbreaks can be driven by the confluence of the cyclic dynamics of rodent populations and weather variability in central China (Tian et al., 2017). In a warming climate, there are growing concerns about the re-emergence of HFRS in HFRS-eliminated regions and emergence of the disease in previously unaffected areas, because cooler areas may become more desirable for rodent breeding and breeding seasons may be extended (Hansen et al., 2015). The 5th IPCC (Intergovernmental Panel on Climate Change) report has suggested the likely increasing risk of HFRS with medium confidence if climate change continues as predicted (Intergovernmental Panel on Climate Change (IPCC), 2014). A better understanding of the association between weather variability and HFRS may provide useful information for early warning of the disease and roughly predict the potential impact of climate change on HFRS incidence.

A recent comprehensive review suggested that although many studies have quantified HFRS-weather associations, few have yielded consistent findings (Hansen et al., 2015), possibly due to the use of different statistical methods and different climate characteristics of the study regions. Furthermore, almost all previously published studies were based on a single area in China. Currently, there is no multi-location study that investigates the HFRS-weather relationship in different climate zones and synthesizes the effect estimates to give a public health perspective. Such is warranted research given that China is a vast and climatically heterogeneous country. In this study, we aim to (1) quantify the associations between weather variability and HFRS transmission in 19 Chinese cities selected from HFRS high risk areas with diverse climatic characteristics; and (2) identify the duration of lagged effects which can provide important information for intervention measures. Findings of this study may provide solid and comprehensive scientific evidence for policy-makers and public health practitioners in the establishment of weather-based HFRS prevention measures in China, East Asia and even internationally.

2. Materials and methods

2.1. Study site

The spatial distribution of hantaviruses in China is characterized by the co-existence of HTNV and SEOV; there is a predominance of HTNV in the north-eastern China and SEOV in the south-western China (Huang et al., 2012; Hansen et al., 2015). Three traditional HFRS high risk provinces with distinct climates in China were selected for analysis. Heilongjiang and Liaoning provinces are located in Northeast China and

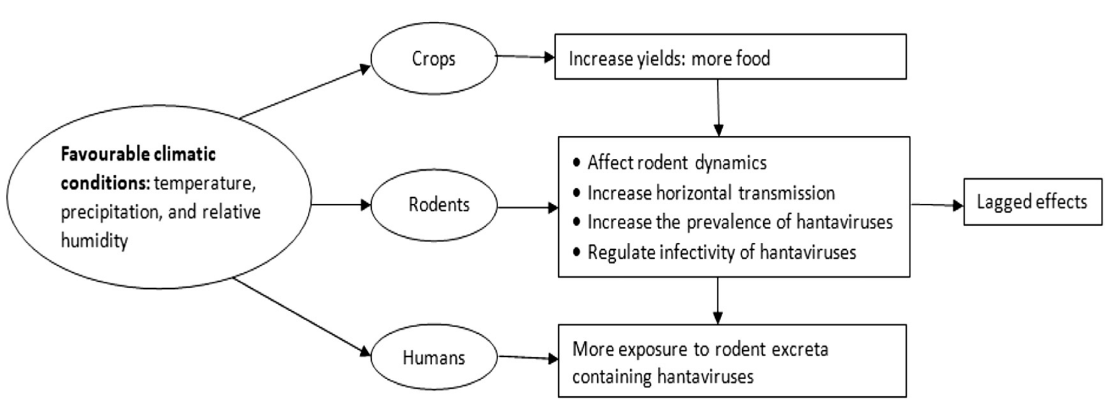

Fig. 1. Flowchart to show how meteorological factors affect HFRS transmission. Favourable weather conditions can regulate rodent population densities by affecting rodent dynamics directly or by increasing crop yields indirectly. Increased rodent population densities can influence the prevalence of hantaviruses and increase horizontal transmission among rodents, which subsequently increases the exposure risk to humans.

have a cold temperate climate. They accounted for about one-third of the country's notified cases of HFRS during 2006–2012 (Zhang et al., 2014). Anhui Province is located in mid-eastern China, which has a humid subtropical monsoon climate. Most of the HFRS cases in Anhui occurred in the low-lying land along the Huai River, such as Yingshang County with an incidence rate being as high as 10 per 100,000 population in the 1980s (Bi et al., 1998). Based on the number of cases reported and the availability of weather data, 19 prefecture-level cities with high incidence rates of HFRS were selected from the above 3 provinces for data analysis. The 19 cities included 3 cities in Anhui (Bengbu, Bozhou, and Fuyang), 7 cities in Heilongjiang (Harbin, Heihe, Jiamusi, Jixi, Mudanjiang, Qiqihar, and Suihua), and 9 cities in Liaoning (Benxi, Chaoyang, Dalian, Dandong, Fushun, Huludao, Jinzhou, Shenyang, and Yingkou), as shown in Fig. 2. Each of the selected prefecture-level cities comprise an urban centre and surrounding rural areas.

2.2. Data collection

De-identified daily reports of HFRS cases from 2005 to 2014 were obtained from the Chinese Center for Disease Control and Prevention. The data were extracted from the China Information System for Disease Control and Prevention (an online reporting system established in 2004). HFRS is a B-category notifiable infectious disease in China according to the Law on the Prevention and Treatment of infectious diseases (National Health and Family Planning Commission of the People's Republic of China, 1991). Thus, within 24 h after diagnosis, the law requires diagnosed cases to be reported online. The variables included in the HFRS dataset mainly comprised age, gender, occupation, dates (disease onset, diagnosis, and reporting), and site of onset. Daily meteorological data for the 19 cities during the study period were downloaded from the China meteorological Data Sharing Service System, including maximum temperature (T_{max}), precipitation, and relative humidity.

Ethical approvals were obtained from the University of Adelaide (Approval No. HS-2013-052), University of South Australia (Approval No. 0000032268), Monash University (Approval No. CF13/3263-2013001642), the Chinese Center for Disease Control and Prevention (Approval No. ICDC-2013002), and Anhui Medical University (Approval No. 2013007).

2.3. Statistical analysis

Descriptive statistics were used to describe the overall epidemiological characteristics of HFRS cases reported in the 3 provinces during the study period. Using date of disease onset, reports of daily HFRS cases from the 19 cities were transformed into an aggregated weekly time series format due to small numbers, and merged with weekly meteorological data from the same city. Similarly, weekly averages of T_{max} and relative humidity, and total weekly precipitation were calculated.

A two-stage method was used to quantify the HFRS-weather associations for the 19 cities (Stukel et al., 2001), as this can synthesize inconclusive or contradictory site-specific results due to small sample sizes or regional variations. In the first stage, the quantitative city-specific HFRS-weather associations for each of the 19 cities were analysed using generalised estimating equation models (GEE) with negative binomial distribution, a log link function and a first order autocorrelation structure. Results for the GEE models are expressed as incidence rate ratios with 95% CIs, and interpreted as percentage change in weekly HFRS cases with the change of meteorological factors. Seasonality and long-term trends were adjusted for by creating indicator variables “month” and “calendar year” in the model (Zhang et al., 2010). The duration of lagged effect was explored by cross-correlation analysis, and an optimal lag length was explored by minimizing the Schwarz's Bayesian information criterion, the Akaike's information criterion and the Hannan–Quinn information criterion, using the Stata command “varsoc”. To compare the effects of different climate zones on HFRS, we also pooled the HFRS-weather effects by province. At the second stage, estimated city-specific HFRS-weather associations were pooled using multivariate random-effects meta-regression models of the first-stage effect estimates (White, 2009). The second-stage meta-analysis was performed using Stata command “mvmeta”. All analyses were conducted with Stata V.13.0 (Stata Corp LP, College Station, Texas, USA). The 0.05 level of statistical significance was adopted for each test.

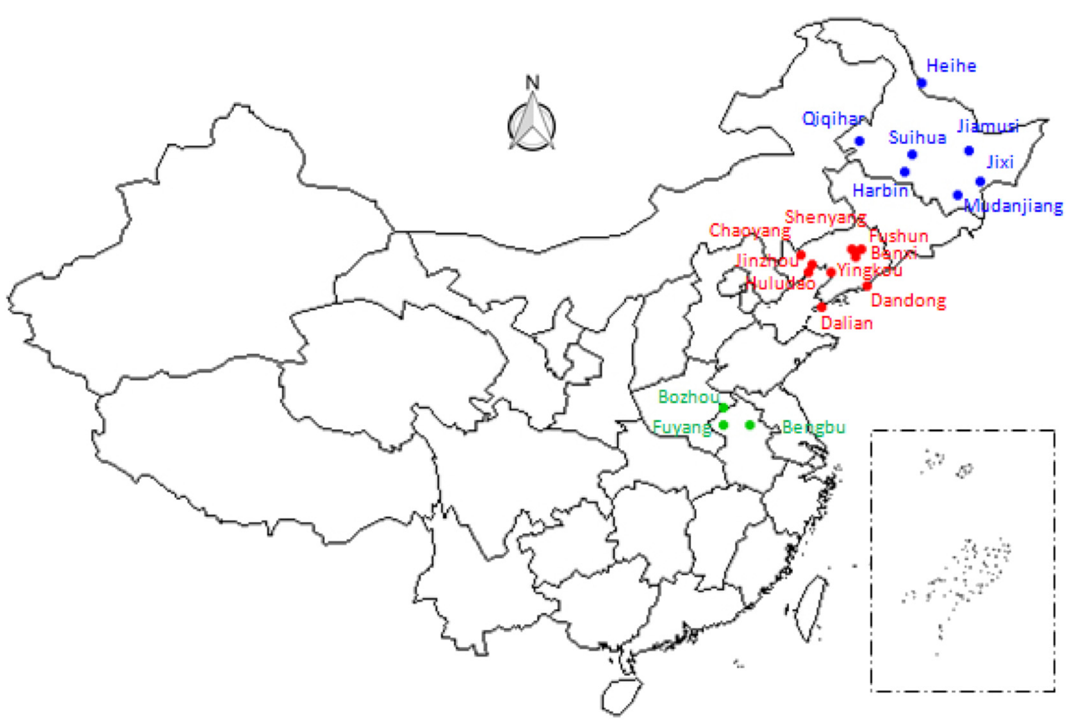

Fig. 2. Location of the 19 cities selected for HFRS-weather data analysis, including 3 cities in Anhui (shown in green), 7 cities in Liaoning (shown in red), and 9 cities in Heilongjiang (shown in blue).

Table 1
Distribution characteristics of HFRS in the 3 provinces (Anhui, Liaoning, Heilongjiang) of China, 2005–2014.

	n	%
Total	39,349	100.0
Gender		
Male	30,209	76.8
Female	9140	23.2
Age		
≤20	2445	6.2
21–39	14,722	37.4
40–59	17,952	45.6
≥60	4230	10.7
Occupation		
Farmer	28,114	71.4
Factory worker	3174	8.1
Student	1000	2.5
Migrant labourer	866	2.2
Household duties and unemployed	2711	6.9
Retiree	758	1.9
Government employee	680	1.7
Other	2046	5.2
Province		
Anhui	1415	3.6
Liaoning	14,277	36.3
Heilongjiang	23,657	60.1

Table 2
Summary statistics of weekly mean maximum temperature, minimum temperature, average relative humidity, and weekly precipitation the 19 cities in China, 2005–2015.

Study site	Maximum temperature (°C) (weekly mean/SD)	Minimum temperature (°C) (weekly mean/SD)	Average relative humidity (%) (weekly mean/SD)	Weekly precipitation (mm) (weekly sum/SD)
Anhui Province				
Bengbu	20.6 (9.9)	12.1 (9.8)	69.6 (14.8)	2.7 (10.1)
Bozhou	20.7 (10.2)	11.9 (9.8)	65.0 (16.2)	2.1 (8.7)
Fuyang	20.7 (10.0)	11.1 (10.0)	71.6 (15.2)	2.3 (9.2)
Heilongjiang Province				
Harbin	10.6 (15.4)	0.3 (15.2)	63.5 (15.6)	1.4 (5.2)
Heihe	7.6 (16.4)	−5.2 (16.7)	67.3 (14.2)	1.4 (4.7)
Jiamusi	8.5 (15.9)	−1.7 (15.5)	70.8 (13.8)	1.4 (4.9)
Jixi	9.9 (14.7)	−0.1 (13.9)	66.1 (15.8)	1.5 (4.9)
Mudanjiang	11.2 (14.8)	−0.4 (14.6)	64.7 (13.3)	1.5 (5.0)
Qiqihar	10.0 (15.7)	−0.7 (15.9)	60.4 (15.7)	1.3 (5.7)
Suihua	10.1 (15.7)	−0.9 (15.6)	64.1 (15.5)	1.3 (5.6)
Liaoning Province				
Benxi	14.2 (13.0)	3.7 (13.2)	64.5 (15.2)	2.3 (7.6)
Chaoyang	10.0 (15.7)	−0.9 (15.6)	64.5 (15.2)	1.3 (5.7)
Dalian	16.3 (12.7)	3.4 (13.1)	53.6 (19.8)	1.2 (5.1)
Dandong	14.2 (11.3)	5.3 (11.7)	70.3 (18.3)	3.0 (11.4)
Fushun	13.8 (13.4)	1.1 (14.3)	70.3 (14.3)	2.2 (7.4)
Huludao	14.5 (11.4)	5.0 (12.2)	66.3 (20.7)	1.8 (10.1)
Jinzhou	15.6 (12.0)	5.8 (12.2)	55.3 (19.6)	1.6 (7.1)
Shenyang	14.2 (13.3)	2.7 (13.9)	66.6 (15.9)	1.9 (6.8)
Yingkou	14.2 (12.0)	6.2 (12.7)	66.9 (14.5)	1.8 (7.9)

SD = standard deviation.

3. Results

Table 1 summarizes the distribution characteristics of HFRS cases in the 3 provinces. During the study period, 2005–2014, a total of 39,349 HFRS cases were reported in the 3 provinces, accounting for 32.3% of all HFRS cases recorded in China. Overall, HFRS incidences demonstrated a downward trend over the study period with a slight rebound after 2010, as shown in Fig. 3. The fluctuating patterns of cases in Heilongjiang and Liaoning provinces were similar, but differed with that in Anhui Province, which remained relatively stable. HFRS seasonality was characterized by a bimodal (spring and winter peaks) distribution pattern. About three quarters of the HFRS cases occurred in males. As shown in Table 1, close to half (45.6%) was observed in the 40–59 age group, followed by the 21–39 years age group (37.4%). Among all occupations, farmers accounted for 71.4% of HFRS cases. Table 2 summarizes the climate characteristics of the selected 19 cities, and shows that the 3 cities in Anhui had warmer and more humid climate than the cities in the other 2 provinces.

Fig. 4 shows the maximum lagged effects of weekly mean T_{max}, average relative humidity, and precipitation on HFRS for the 19 selected cities and the pooled effects for the 3 meteorological factors. Supplementary file 1 shows the city-specific effect estimates at different lags. According to the pooled effects by province, HFRS was more

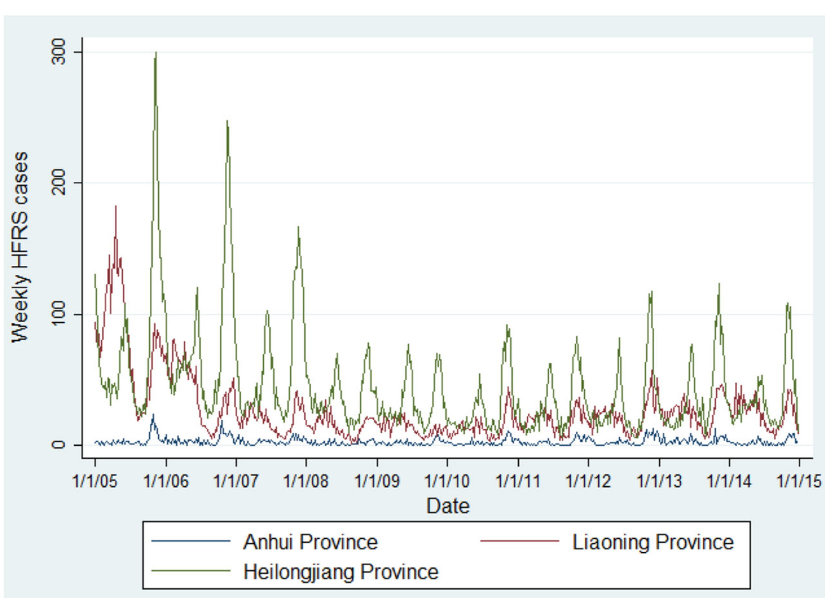

Fig. 3. Trends of weekly HFRS cases reported in the 3 provinces in China, 2005–2014.

sensitive to T_{max}, precipitation, and relative humidity in subtropical regions (Anhui Province) than in temperate regions (Heilongjiang and Liaoning Provinces). Statistically significant positive associations were observed between HFRS and T_{max} in all study sites except Mudanjiang (Heilongjiang Province). A 1 °C increase in weekly mean T_{max} resulted in a 0.6% (95% CI: 0.1%–1.1%) to 10.5% (95% CI: 6.3%–14.7%) increase in HFRS, with corresponding lagged effects ranging from 8 to 34 weeks (Fig. 4-A). Results of meta-regression showed that maximum effect of T_{max} was observed at a lag of 29 weeks, and a 1 °C increase in weekly mean T_{max} was associated with a 1.6% (95% CI: 1.0%–2.2%) increase in HFRS. In Qiqihar, T_{max} was negatively associated with HFRS.

For precipitation (Fig. 4-B), the effect estimates of a 1 mm increase in precipitation peaked at lag 13 to 49 weeks, ranging from a 0.05% (95%CI: 0.02%–0.09%) increase in Suihua (Heilongjiang Province) to a 1.4% (95% CI: 0.9%–1.9%) increase in Chaoyang (Liaoning Province). However, no significant associations were found in Jiamusi and Qiqihar (Heilongjiang Province). Results of meta-regression showed that the maximum effect of precipitation occurred at a lag of 22 weeks, with a 1 mm increase in precipitation being associated with a 0.2% (95%CI: 0.1%–0.3%) increase in HFRS. In terms of relative humidity (Fig. 4-C), the maximum lagged effects ranged from an increase in incidence of 0.02% (95%CI 0.01%–0.03%) at a lag of 49 weeks in Yingkou (Liaoning Province), to 6.1% (95%CI: 3.9% to 8.3%) in Bozhou (Anhui Province) at a lag of 12 weeks. The pooled maximum effect of an increase in average relative humidity was 0.9% (95%CI: 0.5%–1.2%) at lag week 16.

Results of cross-correlation analyses between meteorological factors and HFRS (Supplementary file 2) showed that the duration of lag effects was 4–25 weeks for T_{max}, 5–23 weeks for precipitation, and 9–25 weeks for average relative humidity. The lagged effects of T_{max}, precipitation, and average relative humidity appeared periodically in the following 3–4 epidemic seasons and gradually waned.

4. Discussion

In this study, we quantified the HFRS-weather associations for 19 selected cities, using a two stage method suitable for this multi-location study. Almost all previous studies have focused on one city/county only, using different statistical models, making the comparison of different results problematic (Hansen et al., 2015). To our knowledge, this is the first multi-location HFRS-weather study in the world. Our pooled results suggest that meteorological factors have significant impacts on HFRS incidence in China, although HFRS-weather associations, the timing with maximum effects, and the duration of lagged effects vary by locations. Moreover, we found HFRS was relatively more sensitive to weather variability in subtropical regions (Anhui Province) than that in temperate regions (Heilongjiang and Liaoning Provinces). This finding is useful for guiding HFRS control, resource allocation and developing targeted prevention strategies against climate change-related impact. As a zoonotic infectious disease, HFRS incidence is determined by the complex interactions of multifaceted factors. Although improved public health infrastructure and interventions are the major reason contributing to HFRS reduction, meteorological factors play an important role in HFRS transmission.

In the current study, we found that maximum temperature is the most important meteorological factor for HFRS transmission, based upon the pooled effect estimates (percentage change). However, it should be noted that the importance of meteorological factors in HFRS transmission may vary by location. In this study, no significant HFRS-T_{max} association was observed in Mudanjiang, while a negative HFRS-T_{max} association was found in Qiqihar where the maximum temperature was not very high in summer. By contrast, other studies have shown precipitation to be particularly important for HFRS transmission in Xi'an (Tian et al., n.d.). Temperature not only affects rodent breeding dynamics and activity but also the infectivity of hantaviruses (Bi et al., 2002). Usually, few HFRS cases have been reported in areas with extremely hot or cold weather (Yan et al., 2007). However, it has been reported that the risk of nephropathia epidemica (a mild form of HFRS caused by Puumala virus) increased during cold winters in Northern Sweden, as heavy snow and ground icing may block bank vole access to subnivean space and increase the rodent-human exposure risk (Khalil et al., 2014). Nevertheless, up to 70% of HFRS in China are HTNV and SEOV (Hansen et al., 2015). The most favourable temperature range for rodent breeding has been shown to be around 17 °C (Xiao et al., 2013a; Lin et al., 2014). In cooler climate zones such as Heilongjiang and Liaoning Provinces, a warming climate may allow rodents to survive more easily in winters, shorten the maturity period, increase human-rodent interaction, and thus potentially increase the transmission risk (Zhang et al., 2010; Tian et al., 2005–2012). The re-emergence of HFRS in some cities (e.g. Changchun, Jilin Province) since the early 20th century in northern China underscores the importance of weather variability as a factor in the spread of HFRS and alerts us to the need to monitor HFRS-weather associations more closely (Zhang et al., 2014; Wu et al., 2014).

As mentioned, precipitation is another important meteorological factor affecting HFRS occurrence. In this study a positive precipitation-HFRS association was found in almost all selected cities except Jiamusi and Qiqihar in Heilongjiang Province. Moist and semi-moist soil is necessary for the growth of vegetation and crops in the city outskirts and rural areas. This relates to the abundance of food sources for rodent hosts and potentially the size of the rodent populations. Increased rodent densities can increase the risk of viral transmission among rodents and subsequently result in increased transmission to humans. Some studies have found a causal link between autumn crop production and HFRS incidence (Bi et al., 1998; Bi et al., 2002). Moreover, the majority of HFRS cases in China occurred in low-lying regions and wetlands (Yan et al., 2007). However, excessive precipitation can suppress HFRS transmission by inundating rodent nests and reduced rodent-human contact opportunities (Bi et al., 2002). Therefore, inconsistent results have been reported in the literature.

In the current study, relative humidity was also found to be positively associated with HFRS in China, which is consistent with previous literature (Hansen et al., 2015; Zhang et al., 2010; Li et al., 2013). Relative humidity is not only indicative of moisture levels but can also influence the infectivity and stability of hantaviruses in ex vivo environments (Hardestam et al., 2007). The highest incidence of HFRS has been reported to be in semi-humid areas or in mountainous regions with a humid or semi-humid climate in China (Lin et al., 2007).

The association between weather variability and vector/rodent-borne infectious diseases is characterized with non-linearity and lagged effect. Usually, there is a reversed U-shaped curve relationship between meteorological factors and climate-sensitive diseases (Xiang et al., 2017), because extreme weather conditions are detrimental to the intermediate host's population dynamics and inhibit the infectivity and reproduction of pathogens (Hardestam et al., 2007). Therefore, the majority of cases occur at the optimal ranges of weather conditions desirable for the development of agents and viruses (Hansen et al., 2015), and seasonal fluctuations such as a bimodal distribution pattern for HFRS have been shown in this study and other studies in China (Huang et al., 2012; Zhang et al., 2014). Identification of the duration of lagged effects and the lag time with maximum effects is important for early warnings of, and preparedness for, HFRS outbreaks. In this study, we found that maximum lagged effects of meteorological factors occurred between 1 and 6 months, which is consistent with previous findings in China (Hansen et al., 2015; Zhang et al., 2010; Tian et al., 2005–2012; Xiao et al., 2013b). The minimum time (1 month) required for a lag effect is coincidently equivalent to the rodents' gestation period, although there are many factors affecting the transmission of hantaviruses to the juvenile rodents (e.g. maternal antibodies). Identification of the period that maximum lag effects occurred is useful for HFRS early warning, control and prevention. An important new finding was that lagged effects did not end after an epidemic season but waned gradually in the following 3–4 epidemic seasons which is

approximately equivalent to the lifespan of *Rattus norvegicus* (The Animal Ageing and Longevity Database (AnAge), 2014). As to the reasons of prolonged lagged effects, further research is needed. From the perspective of HFRS control and prevention, relevant intervention measures should not be stopped completely and public health staff need to be vigilant and maintain prevention measures following epidemics.

This study has several limitations. First, HFRS occurrence is the outcome of complex interactions between humans, vectors/reservoir hosts, the agent, and preventive measures. Evidence has shown that non- meteorological factors such as socioeconomic status, urbanization, population immunity level, occupation, and entomological indicators (e.g. rodent intensity) also play an important role in HFRS transmission (Hansen et al., 2015; Bi et al., 2005). However, in this study we did not take these factors into account. As the coverage of HFRS vaccination was relatively stable during the study period (Huang et al., 2012; Zou et al., 2016; Xiao et al., 2014), the impact of immunity and community vaccination on HFRS-weather association is minimal. Nevertheless, caution should be exercised if using meteorological factors alone to predict future HFRS risk. Second, HTNV or SEOV infections were not distinguished because the current commercial immunological test kits to identify hantaviruses do not discriminate between these two separate viruses. The epidemic peak seasons for HTNV and SEOV infections

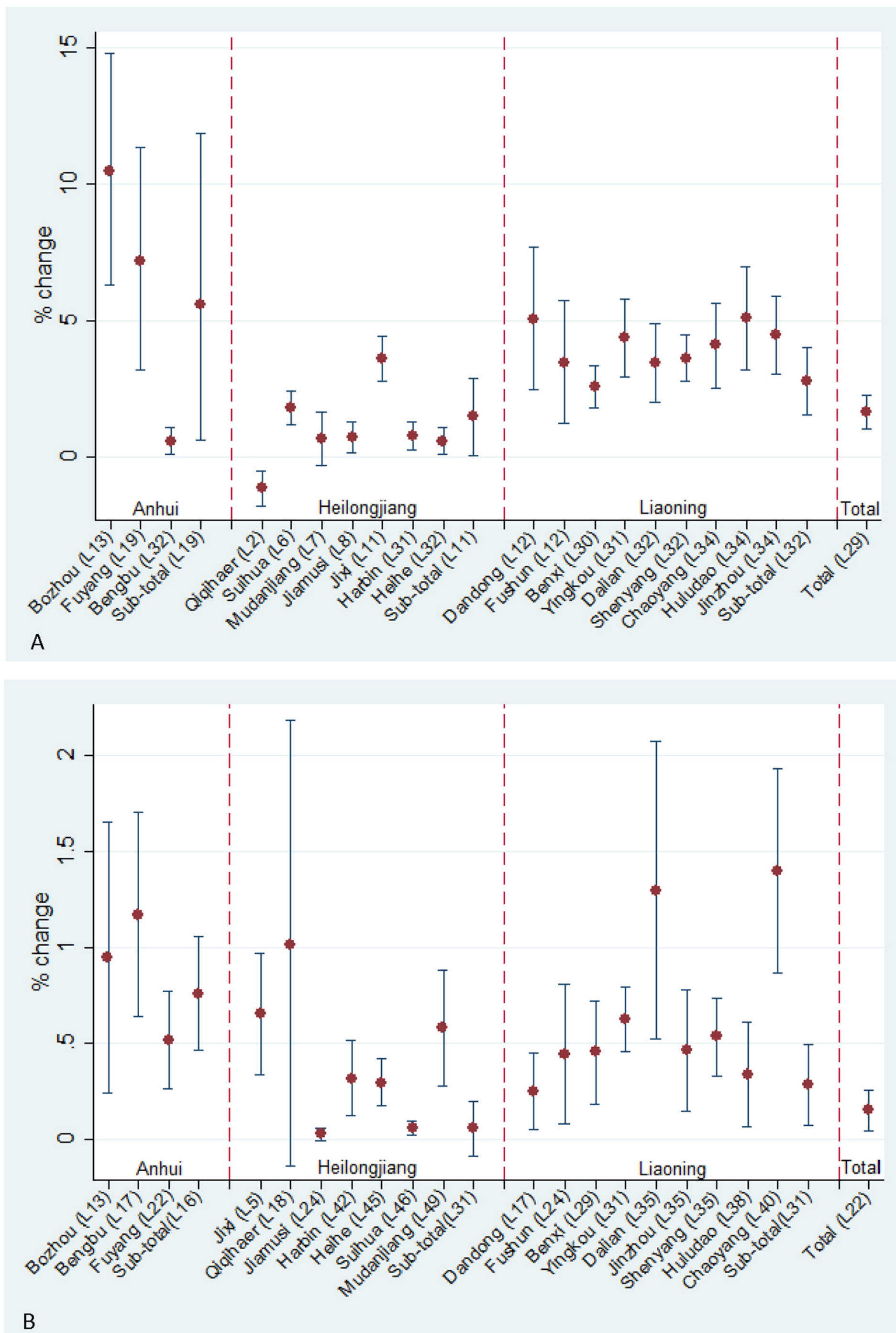

Fig. 4. The y-axis represents the percent change of weekly HFRS with the change of weekly mean maximum temperature (°C) (A), precipitation (mm) (B), and average relative humidity (C) in the 19 selected cities and pooled effects in China, 2005–2014. The x-axis represents the lags with the largest effects for the three meteorological factors. "L" = lag, refers to the lag of weeks with the greatest effects. Sub-total is the pooled effect by province.

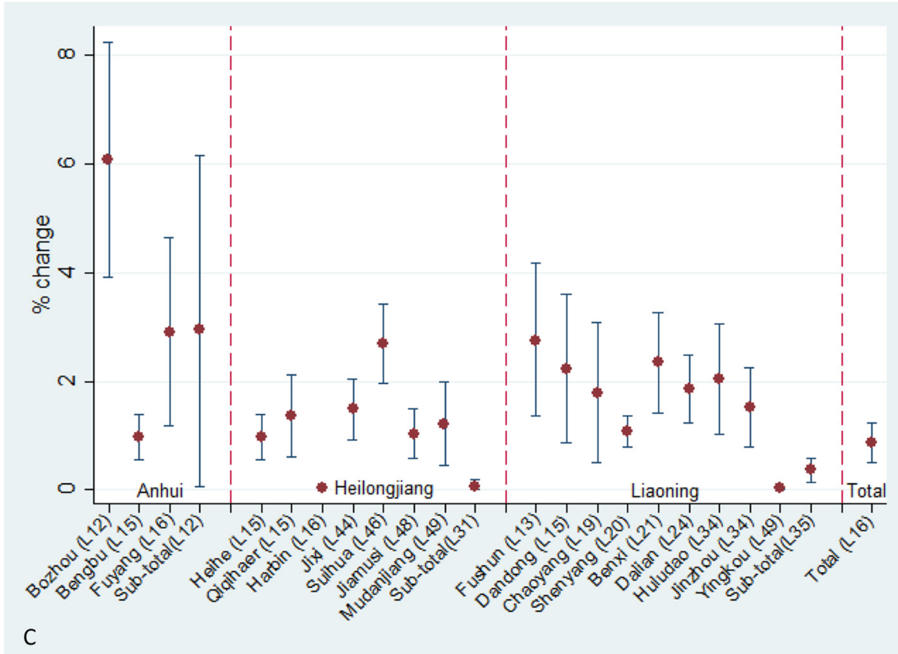

Fig. 4 (*continued*).

were spring and autumn-winter, respectively (Zhang et al., 2014). Not separating the two viruses may affect the accuracy of the HFRS-weather association estimates. As HTNV infections mainly occur in rural areas while SEOV infections are in urban regions, weather variability may have more impact on HTNV than SEOV due to the modifying effects of urban environments. Third, under-reporting is an inherent limitation of historical surveillance data analysis, although it has decreased significantly since the launch of a national infectious diseases online reporting system in 2004 and quality inspection every year by local health departments (Shi et al., 2006). The decrease of under-reporting during the study period may lead to an underestimation of the HFRS-weather association.

5. Conclusions

Meteorological factors, particularly maximum temperature, play an important role in HFRS transmission in China. However, HFRS-weather associations, the timing of maximum effects, and the duration of lagged effects could extend to several years, but vary by region. HFRS early warning and forecasting should be site-specific, taking local meteorological and non- meteorological characteristics into account. The long duration of lagged effects indicates the necessity of continuous interventions even after the epidemics. In addition to vaccination, the medium-short term effective control of rodent populations is important for reducing the estimated effects of meteorological factors on HFRS; while long-term strategies to mitigate climate change need to be developed.

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References

Bi, P., Wu, X., Zhang, F., Parton, K.A., Tong, S., 1998. Seasonal rainfall variability, the incidence of hemorrhagic fever with renal syndrome, and prediction of the disease in low-lying areas of China. Am. J. Epidemiol. 148, 276–281.

Bi, P., Tong, S., Donald, K., Parton, K., Ni, J., 2002. Climatic, reservoir and occupational variables and the transmission of haemorrhagic fever with renal syndrome in China. Int. J. Epidemiol. 31, 189–193.

Bi, P., Parton, K.A., Tong, S., 2005. El Nino-Southern Oscillation and vector-borne diseases in Anhui, China. Vector Borne Zoonotic Dis. 5, 95–100.

Hansen, A., Cameron, S., Liu, Q., Sun, Y., Weinstein, P., Williams, C., et al., 2015. Transmission of haemorrhagic fever with renal syndrome in China and the role of climate factors: a review. Int. J. Infect. Dis. 33, 212–218.

Hardestam, J., Simon, M., Hedlund, K., Vaheri, A., Klingström, J., Lundkvist, Å., 2007. Ex vivo stability of the rodent-borne Hantaan virus in comparison to that of arthropod-borne members of the Bunyaviridae family. Appl. Environ. Microbiol. 73, 2547–2551.

Huang, X., Yin, H., Yan, L., Wang, X., Wang, S., 2012. Epidemiologic characteristics of haemorrhagic fever with renal syndrome in Mainland China from 2006 to 2010. Western Pac. Surveill. Response J. 3, 12–18.

Intergovernmental Panel on Climate Change (IPCC), 2014. Climate Change 2014 (the fifth assessment report): Impacts, adaptation and vulnerability. Available from:. http://www.ipcc.ch/report/ar5/wg2/, Accessed date: 8 June 2017.

Khalil, H., Olsson, G., Ecke, F., Evander, M., Hjertqvist, M., Magnusson, M., et al., 2014. The importance of bank vole density and rainy winters in predicting nephropathia epidemica incidence in Northern Sweden. PLoS One 9:1–7. https://doi.org/10.1371/journal.pone.0111663.

Li, C.-P., Cui, Z., Li, S.-L., Magalhaes, R.J.S., Wang, B.-L., Zhang, C., et al., 2013. Association between hemorrhagic fever with renal syndrome epidemic and climate factors in Heilongjiang Province, China. Am. J. Trop. Med. Hyg. 89, 1006–1012.

Li, S., Ren, H., Hu, W., Lu, L., Xu, X., Zhuang, D., et al., 2014. Spatiotemporal heterogeneity analysis of hemorrhagic fever with renal syndrome in China using geographically weighted regression models. Int. J. Environ. Res. Public Health 11, 12129–12147.

Lin, H., Liu, Q., Guo, J., Zhang, J., Wang, J., Chen, H., 2007. Analysis of the geographic distribution of HFRS in Liaoning Province between 2000 and 2005. BMC Public Health 7, 207. https://doi.org/10.1186/1471-2458-7-207.

Lin, H., Zhang, Z., Lu, L., Liu, Q., 2014. Meteorological factors are associated with hemorrhagic fever with renal syndrome in Jiaonan County, China, 2006–2011. Int. J. Biometeorol. 58, 1031–1037.

National Health and Family Planning Commission of the People's Republic of China, 1991. Law on the Prevention and Treatment of Infectious Diseases.

National Health and Family Planning Commission of the People's Republic of China, 2016. National Morbidity and Mortality of Notifiable Infectious Diseases in 2016. Available from:. http://www.nhfpc.gov.cn/jkj/s3578/201702/38ca5990f8a54ddf9ca6308fec406157.shtml, Accessed date: 23 May 2017.

Sanfeliu, M.R., 2012. Microevolution of Puumala Hantavirus in its Host, the Bank Vole (Myodes Glareolus). University of Helsinki and the Finnish Forest Research Institute Available from:. https://www.researchgate.net/publication/282867889_Microevolution_of_Puumala_hantavirus_in_its_host_the_bank_vole_Myodes_glareolus, Accessed date: 16 September 2017.

Shi, X., Ma, J.Q., Wang, L.P., Zhang, C.X., Guo, Q., Q, X.P., et al., 2006. Analysis of underreporting for notifiable infectious diseases in China, 2005 (in Chinese). Diseases Surveillance. 21, pp. 493–496.

Stukel, T.A., Demidenko, E., Dykes, J., Karagas, M.R., 2001. Two-stage methods for the analysis of pooled data. Stat. Med. 20, 2115–2130.

The Animal Ageing and Longevity Database (AnAge), 2014. AnAge Entry for *Rattus norvegicus*: Lifespan, Ageing, and Relevant Traits. Available from:. http://genomics.senescence.info/species/entry.php?species=Rattus_norvegicus, Accessed date: 9 June 2017.

Tian, H.Y., Yu, P.B., Luis, A.D., Bi, P., Cazelles, B., Laine, M., et al., 2005–2012. Changes in rodent abundance and weather conditions potentially drive hemorrhagic fever with renal syndrome outbreaks in Xi'an, China. PLoS Negl. Trop. Dis. https://doi.org/10.1371/journal.pntd.0003530.

Tian, H., Yu, P., Cazelles, B., Xu, L., Tan, H., Yang, J., et al., 2017. Interannual cycles of Hantaan virus outbreaks at the human–animal interface in Central China are controlled by temperature and rainfall. PNAS 114, 8041–8046.

White, I.R., 2009. Multivariate random-effects meta-analysis. Stata J. 9, 40–56.

Wu, J., Wang, D.-D., Li, X.-L., de Vlas, S.J., Yu, Y.-Q., Zhu, J., et al., 2014. Increasing incidence of hemorrhagic fever with renal syndrome could be associated with livestock husbandry in Changchun, Northeastern China. BMC Infect. Dis. 14 (1). https://doi.org/10.1186/1471-2334-14-301.

Xiang, J., Hansen, A., Liu, Q., Liu, X., Tong, M.X., Sun, Y., et al., 2017. Association between dengue fever incidence and meteorological factors in Guangzhou, China, 2005–2014. Environ. Res. 153, 17–26.

Xiao, H., Lin, X., Gao, L., Huang, C., Tian, H., Li, N., et al., 2013a. Ecology and geography of hemorrhagic fever with renal syndrome in Changsha, China. BMC Infect. Dis. 13, 305. https://doi.org/10.1186/1471-2334-13-305.

Xiao, H., Gao, L.D., Li, X.J., Lin, X.L., Dai, X.Y., Zhu, P.J., et al., 2013b. Environmental variability and the transmission of haemorrhagic fever with renal syndrome in Changsha, People's Republic of China. Epidemiol. Infect. 141, 1867–1875.

Xiao, D., Wu, K., Tan, X., Yan, T., Li, H., Yan, Y., 2014. The impact of the vaccination program for hemorrhagic fever with renal syndrome in Hu County, China. Vaccine 32, 740–745.

Yan, L., Fang, L.Q., Huang, H.G., Zhang, L.Q., Feng, D., Zhao, W.J., et al., 2007. Landscape elements and Hantaan virus-related hemorrhagic fever with renal syndrome, People's Republic of China. Emerg. Infect. Dis. 13, 1301–1306.

Zhang, Y.Z., Zou, Y., Fu, Z.F., Plyusnin, A., 2010. Hantavirus infections in humans and animals, China. Emerg. Infect. Dis. 16, 1195–1203.

Zhang, W.Y., Guo, W.D., Fang, L.Q., Li, C.P., Bi, P., Glass, G.E., et al., 2010. Climate variability and hemorrhagic fever with renal syndrome transmission in Northeastern China. Environ. Health Perspect. 118, 915–920.

Zhang, S., Wang, S., Yin, W., Liang, M., Li, J., Zhang, Q., et al., 2014. Epidemic characteristics of hemorrhagic fever with renal syndrome in China, 2006–2012. BMC Infect. Dis. 14: 384. https://doi.org/10.1186/1471-2334-14-384.

Zou, L.X., Chen, M.J., Sun, L., 2016. Haemorrhagic fever with renal syndrome: literature review and distribution analysis in China. Int. J. Infect. Dis. 43, 95–100.